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False-positives in spontaneous reporting: should we worry about them?

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1 Spontaneous reporting remains the most used and, undoubtedly, the most cost-effective approach for the identification of adverse drug reactions (ADRs). Most of the limitations of this method are well recognised but the possibility of receiving false-positive reports of coincidental drug-event associations has received little attention.

2 In this paper we propose a method based on the Poisson distribution for computing the maximum number of reports of an ADR that could be expected to be reported coincidentally. Three parameters are required: (i) the background risk of the event in the reference population, (ii) the total number of patients treated with the drug considered and, (iii) the proportion of cases that have been reported to the pharmacovigilance system.

3 For most empirical situations occurring in the post-marketing surveillance setting, the expected number remains low and only a maximum of one to three cases could be accepted as possibly coincidental.

4 For rare adverse events such as agranulocytosis or toxic epidermal necrolysis, coincidental associations are so unlikely that a number of reports greater than three constitutes a strong warning and requires further investigation.

5 These findings suggest that for rare events, reports of coincidental drug-event associations are too unlikely to be considered as an important limitation of spontaneous reporting.

Keywords spontaneous reporting pharmacovigilance Poisson distribution adverse drug reactions

Introduction

Spontaneous reporting is undoubtedly the most cost-effective approach for the post-marketing identification of new adverse drug reactions (ADRs) [1]: the surveillance is conducted on the entire population of treated patients and is not restricted to a single *a priori* hypothesis. Unfortunately, three major limitations jeopardise the validity of inferences based on spontaneous reports:

(i) under-reporting: only a variable proportion of ADR cases that have occurred during a given time period are reported by physicians [2]. The proportion of reported cases is invariably unknown and may vary considerably. This is affected by numerous factors such as severity and novelty of the reaction, time since the launch of the drug and media interest [3];

(ii) possibility that the characteristics of reported cases differ from those of non-reported cases (in terms of severity, time to onset, risk factors etc.);

(iii) difficulties in describing the population of users and patterns of drug exposure. Most often, the interpretation of reported data requires complementary drug utilisation studies before decision-making [4].

Thus, the validity of incidence rates calculated on the basis of spontaneously reported data is often questionable and the risks associated with drug treat-

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ments are often underestimated [5]. Conversely, it has been claimed that, in some reported cases, the occurrence of the event during drug treatment may be purely coincidental [6]. This could, in part, counterweigh the effects of under-reporting. Indeed, with the exception of some drug-specific diseases or symptoms such as fixed eruption, the risk in unexposed patients (background risk) is never null. The reporting of some coincidental drug-event associations is therefore expected [7].

The aim of this paper is to determine how likely coincidental associations are to occur in the post-marketing surveillance setting. The probability of receiving a given number of coincidental reports is estimated for different values of the background risk, the number of treated patients and the magnitude of under-reporting of ADR. As in any observational design, a number of reports exceeding the expected number of coincidental reports is indicative of an association but does not necessarily imply causality.

Methods

Consider a period of time during which a total number of patients n have been treated with a given drug. If p is the background risk of presenting with the event in a similar but unexposed population, the expected number of coincidental associations among treated patients during the period considered is $n.p$.

If r is the assumed percentage of cases that are reported, the expected number of reports of coincidental associations is:

$$m = n.p.r$$

In the context of post-marketing surveillance, the number of treated patients (n) is expected to be large and the number of coincidental reports (m) small. Thus, if data on the value of n, p and r, for a given period of time, are available (or if assumptions can be made), the probability $P(k)$ of receiving k coincidental reports can be calculated using the Poisson distribution [8]:

$$P(k) = \frac{e^{-m} m^k}{k!}$$

and the cumulative probability $P(\geq k)$ of receiving at least k coincidental reports is:

$$P(\geq k) = 1 - (P_0 + P_1 + \ldots + P_{k-1})$$

Considering an alpha error of 5%, it is then possible, for a given value of m, to calculate the critical value of k for which $P(\geq k)$ becomes smaller than 0.05 (i.e. the maximum number of reports one can accept as coincidental).

Because the proportion of reported cases is by definition unknown, a sensitivity analysis was conducted with different theoretical values. These calculations were based on a number (n) of 300,000 patients treated during the reference period, a proportion of reported cases (r) ranging from 0.5 to 100%, and three different adverse events of concern in drug safety:

(i) toxic epidermal necrolysis (TEN) with a background risk p of 1.2 per million inhabitants and per year [9];

(ii) agranulocytosis with $p = 6$ per million inhabitants and per year [10];

(iii) acute hepatic injury (excluding obvious viral causation) with $p = 24/100,000$ per year [11].

An average duration of treatment of 3 months with the specified drug was considered. Consequently, the expected number $n.p.$ of coincidental associations during the 3 month period among the $n = 300,000$ treated patients was the following:

TEN: $300,000 \times 1.2/10^6 \times 3/12 = 0.09$;
agranulocytosis: $300,000 \times 6/10^6 \times 3/12 = 0.45$;
acute hepatic injury: $300,000 \times 24/10^5 \times 3/12 = 18$.

These figures must be multiplied by the percentage of reported cases r to obtain the expected number of reports m.

Results

Table 1 gives the minimal value of the Poisson parameter m for which the probability $P(\geq k)$ of receiving at least k coincidental reports becomes greater than 0.05. For instance, among all reports received, nine may be considered as coincidental if it can be assumed that $m = n \times p \times r$ is at least 4.70. Conversely, if the estimate of m does not exceed 1.98, one can accept only a maximum of five coincidental associations among the reports.

Table 2 gives the probability of receiving at least one report of a coincidental drug-event association for each of the three types of event when r ranges from 0.5 to 100%. Table 3 shows the maximum number of coincidental reports one can accept (i.e. the value of k for which $P(\geq k)$ becomes smaller than 0.05) in the specified conditions. For example, for TEN, even if all cases that occurred were reported, only one report can be considered as coincidental no

Table 1 Critical value of the expected number of reports (m) for which the probability of receiving at least k (from 1 to 12) case reports becomes higher than 0.05 (calculation with the Poisson formula)

k	1	2	3	4	5	6	7	8	9	10	12
m	0.05	0.36	0.82	1.37	1.98	2.62	3.29	3.99	4.70	5.43	6.93

matter how many have been received. However, for most common conditions, such as liver injury, it is almost certain that at least one coincidental report will be received.

Discussion

One of the main drawbacks of spontaneous reporting is the absence of a control group and, consequently, the impossibility of knowing the background risk among unexposed patients. Thus, the reported cases could include coincidental drug-event associations and not only cases induced by the drug treatment. The first step of the analysis is to verify that the reported cases are real *drug-event associations*. This requires to ascertain that (i) the patient presented the symptoms specified in the case definition, (ii) he was effectively treated by the drug considered, (iii) the onset of the event was subsequent to the initiation of drug treatment (or to the interruption of the treatment if a withdrawal mechanism is suspected). Once these criteria have been fulfilled, the next step would be to rule out coincidental associations.

It can be deduced from Table 1 that the reporting of more than two drug-event associations requires that the expected number m be greater than 0.5. In most empirical situations, m is expected to be smaller because of under-reporting and of the generally low background incidence of events potentially unexpected (Type B) reactions. Considering the example of agranulocytosis, under the specified conditions (300, 000 patients treated during 3 months), m equals 0.45 and 0.045 if 100% or 10% of cases were reported, respectively. As shown in Table 3, among all reports only two can be considered as coincidental. Consequently, a larger number of reports would allow to reject the null hypothesis that the risk of agranulocytosis in exposed equals the risk in unexposed. For instance, the reporting of 12 cases considered to be coincidental can only occur if m is at least 6.93 (Table 1); using the figure of 300,000 treated patients, this corresponds to a risk for a 3 month period of $6.93/300{,}000 = 23.1/10^6$ if all cases were reported and $6.93/300{,}000 \times 25/100 = 92.4/10^6$ if 25% of cases were reported. Under the optimistic hypothesis of a complete reporting, this risk appears to be 15.4 times greater than the reference: $6/10^6 \times 3/12 = 1.5$. This is a conservative estimate as the proportion of cases that are identified and then reported is usually smaller than 10%, even for serious reactions [12, 13].

Table 2 Probability of receiving at least one report of a coincidental drug-event association when 300 000 patients have been treated during 3 months and the percentage of reported cases r varies from 0.5 to 100%

Percentage of reported cases	*TEN*	*Agranulocytosis*	*Liver injury*
100	0.086	0.362	1
75	0.065	0.286	1
50	0.044	0.201	1
25	0.022	0.106	0.989
10	0.009	0.044	0.835
5	0.004	0.022	0.593
1	0.001	0.004	0.165
0.5	0	0.002	0.086

Table 3 Maximum number of reports that can be considered as coincidental when 300 000 patients have been treated during 3 months and the percentage of reported cases r ranges from 0.5 to 100%. If a greater number of reports is received, then one can reject the null hypothesis that the drug-event association is coincidental with a 95% confidence

Percentage of reported cases	*TEN*	*Agranulocytosis*	*Liver injury*
100	1	2	25
75	1	1	21
50	0	1	14
25	0	1	8
10	0	0	4
5	0	0	3
1	0	0	1
0.5	0	0	0

For events characterised by a very low background incidence such as TEN, the reporting of more than one case allows to reject the null hypothesis that the risk in the exposed equals the risk in unexposed patients (Table 3) and constitutes a strong warning.

It should be kept in mind that the rejection of the null hypothesis (the risk is the same for treated and non-treated individuals) allows to conclude to a significant association between exposure to the drug and occurrence of the event. However, this does not necessarily involve a causal relationship. Possible confounders should be taken into account (e.g. the treated disease may be associated with a higher risk of presenting with the symptom) and discussed after further investigation.

For more common events such as liver injuries, a larger number of coincidental associations is expected and case by case causality assessment could be useful to rule them out (Table 3). However, for such common conditions, the proportion of reported cases is expected to be lower than for rare events and the maximum number of false positives is consequently reduced (e.g. eight if 25% of cases are reported: Table 3). Moreover, for many drugs the effective duration of use is probably shorter than 3 months which reduces further the expected number of coincidental reports. For instance, on the basis of a duration of 1 month, the maximum number of coincidental reports would be six, four and two if 50, 25 and 10% of cases are reported, respectively.

Conclusion

The probability of a significant number of coincidental drug-event associations to be reported remains null or low unless the symptom is very common in

the population and the number of treated patients is extremely large. For rare adverse events, such as blood dyscrasias and most type B reactions, receipt of more than three reports is highly unlikely to be coincidental and constitutes an important signal requiring further investigation. Even for more common events, the number of coincidental reports remains low because of under-reporting.

These findings indicate that, for rare events, coincidental drug-event associations are so unlikely that they should be treated only as a marginal issue.

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